Remarks

Applicants respectfully request entry of the Amendment and reconsideration of the claims.

Applicants have amended claim 6 with support at pages 6 to 7. Please cancel claims 14 and 15 without prejudice. Applicants reserve the right to file one or more continuation applications to claim the cancelled subject matter.

Applicants respectfully request reconsideration and withdrawal of the pending rejections under 35 U.S.C. §§ 102(b), 103(a), and 112, first paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 6, 8-17, 21-25 and 31 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner specifically alleges a lack of written description since the constituents of the composition are claimed only by functionality without physical or chemical structure.

Solely for the purpose of advancing the present application to allowance, claim 6 has been amended to recite the "hepatic glutathione increasing compound" as being at least one of N-acetylcysteine, cysteine esters, L-2-oxothiazolidine-4-carboxolate (OTC), gamma glutamylcysteine and its ethyl ester, glutathione ethyl ester, glutathione isopropyl ester, lipoic acid, cystine, cysteine, methionine, or S-adenosylmethionine (SAMe) and to recite the "nitric oxide donor" ("donors" amended to "donor") as being at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, nitrosylated cysteine esters, nitrosylated L-2-oxothiazolidine-4-carboxolate (NOTC), nitrosylated gamma glutamylcysteine and its ethyl ester, nitrosylated glutathione ethyl ester, nitrosylated glutathione isopropyl ester, nitrosylated lipoic acid, nitrosylated cysteine, nitrosylated cystine, nitrosylated methionine, or nitrosylated S-adenosylmethionine. Support for the amendment can be found at page 6, last paragraph, bridging page 7, 4th paragraph of the specification. By this amendment, Applicant provides compounds of known structure to claim 6. By definition, the dependent claims incorporate the structures provided by independent claim 6.

In view of the amendment to claim 6, Applicants respectfully request removal of this rejection.

Rejection under 35 U.S.C. § 102(b)

1. Buckley & Whorton. The Examiner rejects claims 6 and 8 under 35 U.S.C. § 102(b) as allegedly anticipated by Buckley & Whorton (*Am. J. Physiol. Cell Physiol.*, 279, C1168-1176 (2000). The Examiner asserts that Buckley & Whorton disclose administration of SIN-1 to endothelial cells and smooth muscle cells that encompass claim 6. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants respectfully traverse this rejection.

Claim 6 has been amended as discussed above. As amended, claim 6 requires a hepatic glutathione increasing compound, wherein the hepatic glutathione increasing compound is at least one of N-acetylcysteine, cysteine esters, L-2-oxothiazolidine-4-carboxolate (OTC), gamma glutamylcysteine and its ethyl ester, glutathione ethyl ester, glutathione isopropyl ester, lipoic acid, cystine, cysteine, methionine, or S-adenosylmethionine (SAMe). Claim 6 also requires hepatic nitric oxide donor for reducing insulin resistance, wherein the hepatic nitric oxide donor is at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, nitrosylated cysteine esters, nitrosylated L-2-oxothiazolidine-4-carboxolate (NOTC), nitrosylated gamma glutamylcysteine and its ethyl ester, nitrosylated glutathione ethyl ester, nitrosylated glutathione isopropyl ester, nitrosylated lipoic acid, nitrosylated cysteine, nitrosylated cystine, nitrosylated methionine, or nitrosylated S-adenosylmethionine.

Buckley & Whorton fail to disclose each and every element of the claimed composition. The cited reference does not disclose a composition containing both required elements.

The Examiner contends that treating the cells with SIN-1 and washing the cells with HEPES buffer containing a supplemental amount of cysteine reads on instant claims 6 and 8. The Examiner also contends that the composition does not have to contain the glutathione increasing compound and the nitric donor at the same time. Applicants respectfully disagree.

> "Comprising" is a term of art used in claim language which means that ***the named elements are essential***, but other elements may be added and still form a construct within the scope of the claim. [***emphasis added***] MPEP 2111.03; Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501 (Fed. Cir. 1997).

Due to the use of the transition term "comprising", it is essential that the composition contains both a glutathione increasing compound and a nitric donor. However, Buckley & Whorton do not recite a composition containing SIN-1 and a hepatic glutathione increasing compound. For at least this reason, Buckley & Whorton do not anticipate claims 6 and 8.

2. Corrales et al. Claims 6 and 8 were also rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Corrales et al. (*Journal of Hepatology*, 31, 887-894 (1999)). The Examiner stated that Corrales et al. disclose administration of D,L,-Buthione S,R-sulfoximine (BSO) and glutathione monoethylester (EGSH) as a permeable derivative of glutathione (GSH). The Examiner alleges that Corrales discloses that BSO is an NO donor. The Examiner further stated that the reference teaches the simultaneous administration of BSO and EGSH prevented the effect of BSO, namely the lowering of hepatic GSH level. The Examiner further stated that the reference teaches that SIN-1 is a nitric oxide donor.

Claim 6 has been amended as discussed above and is restricted to a pharmaceutical composition comprising the combination of at least one of the recited hepatic glutathione increasing compounds, and at least one of the recited nitric oxide donors. Corrales et al. do not disclose a composition that meets each and every limitation as recited in claim 6. For at least this reason, Corrales et al. do not anticipate claims 6 and 8.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 102(b).

Rejection under 35 U.S.C. 103(a)

The Examiner rejects claims 9-17, 21-25 and 31 under 35 U.S.C. § 103(a) as allegedly obvious over Corrales et al. as applied to claim 6 and 8 above, in view of WO 00/19992 (Lautt) and further in view of Mattia, 1998, *Diabetologia*, 41, 1392-1396.

To establish a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court, a combination is

obvious if it is no more than the predictable use of known elements according to their established functions; and there was a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007). Applicants submit that the Examiner does not make a *prima facie* case of obviousness, because all the limitations of the present claims are not taught by the combination of references cited in the Office Action.

The Examiner contends that it would have been obvious to combine the Corrales, Lautt and Mattia references to arrive at the instant claims since Corrales et al. disclose a pharmaceutical composition of BSO (which the Examiner alleges is a NO donor) and EGSH (which the Exmainer alleges is a glutathione increasing compound), Lautt discloses a composition and method for reducing insulin resistance by administration of SIN-1, and Mattia discloses a composition comprising N-acetyl cysteine to treat non-insulin dependent diabetes.

Applicants respectfully disagree. None of the cited references alone or in combination, teach or suggest all of the claimed limitations of claims 9-13, 16-17, 21-25 and 31. As discussed above, claim 6 has been amended and is now restricted to a pharmaceutical composition comprising the combination of at least one of the recited hepatic glutathione increasing compounds, and at least one of the recited nitric oxide donors. Corrales et al. do not teach or suggest the presently claimed pharmaceutical composition. Accordingly, Corrales also does not teach or suggest the use of the pharmaceutical composition according to claim 6 for reducing insulin resistance in a mammalian patient having lower than normal hepatic glutathione levels as defined in independent claim 9.

Contrary to the Examiner's assertion, BSO is not a NO donor. BSO is known in the art as a GSH synthesis inhibitor (see for example, Guarino et al., *Am. J. Physiol Gastrointest Liver Physiol*, 284, G-588-G-594, 2003 and Anderson, Chemico-Biological Interactions, 111-112, 1-14, 1998). This fact is acknowledged in Corrales et al. at page 889, 1st column, first paragraph. The aim of the study reported in Corrales was to investigate the effect of GSH levels on methionine adenosyltransferase (MAT) mediated S-nitrosylation which is associated with pathological conditions such as liver cirrhosis (see for example the abstract, and page 893, 1st column, 1st paragraph).

The authors administered BSO for the purpose of depleting intracellular GSH levels prior to restoration of GSH levels by the subsequent administration of EGSH (see for example, page

889, 1st column). Corrales et al. are silent with respect to administrating a pharmaceutical composition comprising the combination of a hepatic NO donor and a hepatic glutathione increasing compound for the purposes of reducing insulin resistance in mammalian patient having lower than normal hepatic glutathione levels. As BSO is known in the art to decrease intracellular GSH levels, the person skilled in the art desirous of increasing both hepatic NO and GSH levels would not contemplate administering BSO together with a glutathione increasing compound since the person skilled in the art would reasonably predict that the BSO would have the effect of further lowering hepatic glutathione levels in a patient already having lower than normal hepatic glutathione levels. Accordingly, Corrales et al. do not teach or suggest a pharmaceutical composition comprising a NO donor and a glutathione increasing compound useful for reducing insulin resistance.

Since Corrales et al. are silent with respect the treatment of insulin resistance or any other related metabolic disorder, there is no basis to combine Corrales with Lautt and/or Mattia. Furthermore, Lautt and Mattia, alone or in combination, do not teach or suggest administrating a pharmaceutical composition comprising the combination of a hepatic NO donor and a hepatic glutathione increasing compound for the purposes of reducing insulin resistance in mammalian patient having lower than normal hepatic glutathione levels.

Lautt only discloses a method for increasing insulin sensitivity comprising the administration of an effective amount of a compound which stimulates nitric oxide production in the liver. There is no teaching or suggestion that insulin resistance is related to lower than normal hepatic glutathione levels. There is no teaching or suggestion of the use of any glutathione increasing compound for either increasing insulin sensitivity or for reducing insulin resistance. While Mattia does disclose that N-acetycysteine treatment increases intraerythrocytic levels of GSH in otherwise healthy non-insulin dependent diabetics, there is no teaching or suggestion that increased GSH levels are correlated with reduced insulin resistance or any other metabolic disorder, let alone any suggestion that increasing hepatic glutathione levels would be useful for treating insulin resistance.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

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Brian R. Dorn, Ph.D.
Reg. No. 57,395
BRD:dc